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Discussion

Dr Todd K. Rosengart *(Stony Brook, NY)*. The authors are to be congratulated for translating solid experimental laboratory data into a logical extension in clinical Unfortunately, as has been the case on a number of occasions, the human condition has confounded the efforts to reasonably and logically test some of your experimental hypotheses. I have a number of questions; but I'll ask you 4, which I'll ask you one at a time for simplicity.

First, why did you not administer VEGF into an unrevascularized territory so you could take advantage of a low baseline perfusion level as opposed to administering VEGF into the LAD territory? Obviously, this creates potential problems of artifact because of your bypass grafts.

Dr Ruel. This is an excellent question and a point that we had to resolve at the design level of the study. VEGF is a relatively poor angiogenic factor, but it is intimately NO dependent, perhaps more than fibroblast growth factor-2 and hepatocyte growth factor, which are other cytokines that are potentially more robust. We also chose VEGF first because it has been widely studied in humans, and part of this comes from your work as well. We also chose VEGF because it was available from our collaborators in addition to being NO dependent.

On the other hand, we did not want to expose patients to the possibility of ineffective angiogenesis, which could have happened in the VEGF and placebo groups. We thus protected our patients by bypassing all their territories as well as we could, considering that those patients all had diffuse LAD disease.

Furthermore, we had a precise measure of myocardial blood flow. By performing the anterior myocardial bypass at the same target site in every patient, which was the distal LAD, we could focus on the basal, mid, and early distal portions of the anterior wall to isolate the effect of VEGF.

In addition, the performance of baseline PET scanning, which would be repeated at 3 months, early *after* the operation instead of *before* the operation, accounted as best as possible for the confounding effects of CABG.

Dr Rosengart. You mentioned in your article and presentation that you used intraoperative validation or verification that the LAD was suitable for your experimental protocol. Can you go into a little bit more detail on that? Or conversely, did you attempt to use any kind of strict angiographic guidelines to determine whether you'd have a consistent cohort to study?

Dr Ruel. Those patients were screened on the basis of their potential ungraftability. Several of them came from other centers and were referred to us as ungraftable or likely ungraftable.

The intraoperative validation was informal. Initially, the patients were screened and found to have a diffusely diseased LAD; in many cases we thought that a LAD graft would perhaps not be constructible. As many of us know, if you really put your mind to it, you can basically graft anything with a lumen in it. So this is what we did, and we bypassed the initial healthy portion of the LAD, which in all patients corresponded to its most distal portion.

The intraoperative validation was done by a non-investigator cardiac surgeon who confirmed that each patient had diffuse distal disease, but there were no specific radiologic measures to determine eligibility for the trial. As you know, measures of coronary disease diffuseness are controversial, and despite attempts in the literature to develop those, they remain neither well accepted nor used.

Dr Rosengart. Again, in the same regard, you used baseline perfusion assay at days 3 to 5, or even in one case, I guess, day 7 postoperatively. I'd be concerned that this introduced some variability. Although you clearly show a difference between the experimental and control groups, how do you know that the change in perfusion is completely a VEGF effect as opposed to some collateralization occurring because of the bypass?

Dr Ruel. You're absolutely right. Again, your point deals with the issues of doing this study in humans. We had few alternatives. We thought that doing the baseline PET scanning preoperatively would be less precise than doing what we did. However, there are patients for whom undergoing a full PET scan 3 days after a bypass operation is not ideal, especially those, as in this population, who have diffuse coronary disease and may consequently have had a slightly longer operation.

You're absolutely right that VEGF has several effects. Angiogenic cytokines are not only angiogenic but also have acute vascular and other effects. For instance, VEGF results in local vasodilatation and increased permeability. We did see some of these effects on baseline PET scanning and tried to objectively and anatomically account for them as best as possible.

As you know, the onset of action of VEGF and other angiogenic cytokines is usually approximately 2 weeks, so we considered that the first 5 days were relatively protected from most of the angiogenic effects of the protein. It is possible that some patients may have been better responders and their effects started before.

Dr Rosengart. Can you tell us a little bit more about the toxicity, or the purported toxicity, of L-arginine? Is this a real phenomenon or how do we deal with that? If it is real, are there alternatives (which obviously is NO or nitroglycerin) that would be suitable in a clinical arena?

Dr Ruel. I think a lot of researchers are disappointed by the bad press recently attributed to L-arginine because of a single relatively

limited scope trial published about a year ago. The trial dealt with patients who had an acute ST elevation, had no revascularization, and were randomized to receive L-arginine or not.

There may be other ways to modify endothelial function and NO bioavailability. One way, for instance, may be to up-regulate argininosuccinate synthase, which is a specific enzyme that derives endothelial NO synthase from citrulline. So there are ways other than L-arginine to make the myocardial substrate more amenable to the new therapies that we want to see become effective one day.

Notice of Correction

Kondruweit M, Weyand M, Mahmoud FO, Geißdörfer W, Schoerner C, Ropers D, Achenbach S, Strecker T. Fulminant endocarditis caused by *Streptobacillus moniliformis* in a young man. *J Thorac Cardiovasc Surg*. 2007;134:1579-80.

The spelling of the surname of author Walter Geißdörfer was incorrect. The correct spelling is shown in the author line, above.